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Preclinical signs of Parkinson's disease: A possible association of Parkinson's disease with skin and hair features

Neringa Jucevičiūtė[a], Indrė Banaitytė[b], Antanas Vaitkus[b,*], Renata Balnytė[b]

[a] Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, Lithuania
[b] Department of Neurology, Lithuanian University of Health Sciences, Lithuania

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder, characterized by loss of dopaminergic neuromelanin containing neurons in the substantia nigra. Peripheral melanin, found in skin and hair, and neuromelanin appear to have some characteristics in common and share the same precursor for their synthesis; therefore, skin and hair features could be associated with PD. We hypothesize that earlier age at onset of hair greying, greater tendency to sunburn, difficulty tanning and dysregulation of sebum production are more common among PD patients due to genetically determined lower constitutive amounts of melanin and accumulation of α-synuclein in the skin, which leads to disrupted synthesis of peripheral melanin and dysregulated sebum secretion. In order to test this hypothesis 32 PD patients and 35 age and gender matched PD-unaffected individuals were included in a pilot study. The median of age at onset of hair greying was 30% lower in the PD group compared to the control group (35 and 50 years, respectively, $p = 0.002$). Age at onset of hair greying ≤ 41 years predicted the development of PD with 71.0% sensitivity and 70.6% specificity (area under curve = 0.725, 95% confidence interval = 0.601–0.850, $p = 0.002$). Significant differences were found when comparing skin types between PD patients and the control group ($p < 0.001$): dry (n = 14, 43.8%) and oily (n = 9, 28.1%) skin types were the most prevalent among individuals with PD, whereas the majority of control subjects reported having normal skin (n = 24, 68.6%). Differences in tanning ability were also found between the groups ($p = 0.035$): the majority of individuals in the control group (n = 24, 68.6%) and only 12 (37.5%) PD patients reported being able to tan easily. PD patients were also more likely to burn often in comparison to control subjects (n = 21, 65.6% vs n = 10, 28.6%, $p = 0.001$). Our results support the hypothesis that PD is associated with earlier age at onset of hair greying, greater tendency to sunburn, difficulty tanning and non-normal skin type; however these ideas should be evaluated in a large prospective study in order to draw final conclusions. If such work supports our hypothesis, skin and hair features could be included in a risk-score model to identify individuals at high risk of PD in order to diagnose patients prior to the manifestation of motor symptoms and initiate potential neuroprotective treatment when neuronal loss is minimal.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder, characterized by progressive loss of neuromelanin (NM) containing dopaminergic neurons in the substantia nigra (SN) pars compacta and widespread aggregation of the α-synuclein protein [1]. All currently available therapies for PD are symptomatic; however, many potential disease-modifying agents have shown great promise in preclinical studies and are under exploration [2,3]. At the time of motor symptom onset the number of already lost SN dopaminergic neurons is approximately 30% [4] and may even reach 66% [5]; therefore, once the efficiency of neuroprotective drugs is proven, treatment should begin as early as possible, even in the pre-motor phase of PD when neuronal loss is minimal and disease – modifying therapy is expected to be most effective. The presence of motor symptoms is essential for the diagnosis of PD [6], but their onset is preceded by several years of unspecific non-motor symptoms. Even though currently there is no test to diagnose pre-motor PD, promising results have been yielded in studies exploring the potential use of magnetic resonance imaging (MRI) to detect neuromelanin depletion [7] and recent progresses in molecular imaging with positron emission tomography and single-photon emission tomography have offered means of detecting dopaminergic dysfunctions in the pre-motor phase [8]. Therefore, it is of vital importance to identify risk factors for PD as well as pre-motor features of PD with the eventual

* Corresponding author at: Department of Neurology, Lithuanian University of Health Sciences, Eiveniu Str. 2, LT-50009 Kaunas, Lithuania.
E-mail addresses: antanas.vaitkus@kaunoklinikos.lt (A. Vaitkus), renata.balnyte@kaunoklinikos.lt (R. Balnytė).

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aim of diagnosing patients prior to the manifestation of motor symptoms in order to initiate potential neuroprotective treatment. NM appears to share some characteristics with melanin found in the skin and hair, herein, in this article we focus on skin and hair changes as possible pre-motor features of PD, which could prove to be useful when identifying individuals at risk of developing the classical syndrome of PD.

Hypothesis

NM is not the only type of melanin found in the human body. There are parallels between NM and the other two types of melanin pigments, eumelanin and pheomelanin (in this article both are referred to as peripheral melanin), which are synthesized by melanocytes and are present in peripheral tissues, including the hair, the skin and the iris [9]. The first reaction in the synthesis of peripheral melanin and dopamine is the conversion of L-tyrosine to L-dopa, catalysed by tyrosinase in peripheral tissues and by thyroxine hydroxylase in the central nervous system [10]. Unlike peripheral melanin which is synthesized directly from l-tyrosine, NM is produced via oxidation of excess dopamine [11]. Therefore, even though the synthesis of NM, dopamine and peripheral melanin occurs via distinct pathways, they all share the same precursor. Considering this evidence we hypothesize that PD might be associated not only with the depletion of NM containing dopaminergic neurons in the SN pars compacta, but also with disrupted synthesis of peripheral melanin. That being the case, skin and hair characteristics might be pre-motor features of PD or be associated with higher risk of developing PD.

The constitutive pigmentation of skin is determined by the amount of peripheral melanin and its synthesis can also be further stimulated by exposure to ultraviolet (UV) radiation. Peripheral melanin is considered a major photoprotector because it acts as an antioxidant and reduces the penetration of UV radiation, which is the main causative factor in the DNA damage-initiated development of melanoma [12]. While the levels of pheomelanin are very similar between individuals, higher amounts of epidermal eumelanin determine darker skin pigmentation as well as lower sensitivity to UV radiation [13]; thus, are associated with lower risk of melanoma. A recent meta-analysis, which included 24 studies with a total number of 292,275 PD patients, concluded that the odds of developing melanoma for PD patients are increased more than two-fold (odds ratio [OR], 2.43; 95% confidence interval [CI], 1.77–3.32) [14]. One of the possible mechanisms explaining this association might be disrupted UV radiation-induced melanogenesis due to increased expression of α-synuclein in the skin of PD patients, resulting in tyrosinase inhibition [15]. This hypothesis is supported by studies which report that α-synuclein accumulates not only in the central nervous system, but also in the epidermis of PD patients; whereas the expression of α-synuclein is scarce in the skin of individuals diagnosed with atypical parkinsonism and exiguous or even null in neurologically asymptomatic subjects [16,17]. There is also evidence of α-synuclein deposition in dermal nerve fibres of patients with rapid eye movement sleep behaviour disorder (RBD) [18], which is often a prodromal stage of synucleinopathies, including PD [18]. In addition, the same study showed that α-synuclein accumulation is higher among RBD patients with advanced stages of RBD, characterized by hyposmia and diminished striatal dopamine transporter binding [18]. This evidence leads to the conclusion that α-synuclein accumulation in the skin begins several years prior to the development of the classical syndrome of PD, rendering the skin more susceptible to UV radiation. Hypothetically, PD patients might also have genetically determined lower constitutive amounts of eumelanin what would also result in higher sensitivity to UV radiation. Fitzpatrick's classification is the traditional way of determining the response of skin elicited by UV radiation [19]. Skin phototypes I (always burns, unable to tan) to IV (rarely burns, tans easily) are based on an individual's tendency to burn and ability to tan, whereas skin phototypes V-VI are based on constitutive darker pigmentation [19]. Individuals with phototype I have the lowest concentration of epidermal eumelanin, which rises in accordance with increasing skin phototype [20]. Therefore, if PD patients have low amounts of epidermal eumelanin, they should burn more easily and have greater difficulty tanning compared to individuals unaffected by PD.

Not only the constitutive pigmentation of skin, but also hair colour is determined by varying amounts of peripheral melanin. Black to blond hairs contain low and nearly constant concentrations of pheomelanin (0.85–0.99 μg/mg) while eumelanin levels vary greatly and are nearly five times higher in black hairs compared to blond ones (22.2 vs 4.7 μg/mg) [21]. Interestingly, red hairs contain high amounts of pheomelanin and even less eumelanin than blond hairs (4.7 and 3.8 7 μg/mg, respectively) [21]. The hypothesis that PD patients might have genetically determined lower constitutive amounts of eumelanin is supported by a prospective study which included a total number of 132,302 individuals and concluded that individuals with red hair are at the highest risk of developing PD, which decreases with increasing darkness of hair colour [22]. Melanogenesis in hair follicles does not remain constant and decreases with age, resulting in senile greying. Decreased tyrosinase activity due to reactive oxygen species is one of the multiple theories proposed to explain this process [23]. There is a possibility that the inhibition of tyrosinase by α-synuclein [15] might result in earlier onset of hair greying due to decreased melanogenesis in hair follicles. It is also of interest to note that darkening of grey hair in PD patients following L-dopa therapy has been reported [24–26].

The hypothesis that PD might be associated with constitutive amounts of eumelanin in the skin fits the observed racial disparities in the prevalence of PD. Even though delay in diagnosis and under-diagnosis due to lack of healthcare access complicate the assessment of the prevalence of PD [27], African-Americans have been reported to be half as likely to be diagnosed with PD as Caucasian-Americans [28]. Consistent findings were reported in a study of the US Medicare Database which included 450,000 PD cases per year, with data spanning 10 years [27]. This large-scale study concluded that PD is approximately twice as common in Caucasian-Americans as it is in African-Americans or Asian-Americans; age-standardized PD prevalence (per 100 000) was 2168, 1036 and 1139, respectively [29]. In addition, ethnic origin is associated not only with skin pigmentation, but also with natural hair colour and age at onset of hair greying. It is approximated that the average age at onset of hair greying is mid-30 s for Caucasians and mid-40 s for individuals of African descent [30]. Another study also concluded that the incidence of hair greying appears to depend mainly on the ethnic origin and reported that individuals of Asian and African descent have less grey hair than those of the same age of Caucasian descent [31]. These results support the hypothesis that earlier onset of hair greying is associated with PD; however, due to lack of data on the link between hair features and PD in groups of individuals of different ancestry, this association seems far-fetched. Nevertheless, based on our hypothesis, the inhibition of tyrosinase by α-synuclein should result in earlier onset of hair greying in all PD patients despite their ethnicity; however, adjustment for major ancestry of patients should be made when evaluating the age at onset of hair greying due to its variability in individuals of different descent. PD could also be associated with skin type, which is determined by the amount of sebum secreted by sebaceous glands. Higher values of sebum excretion have been reported in PD patients compared to healthy subjects [32] and this could be the reason behind the high prevalence of seborrheic dermatitis among PD patients. Seborrheic dermatitis can precede the development of PD; the odds of developing PD for patients diagnosed with seborrheic dermatitis are increased by 69% (OR = 1.69, 95% CI = 1.36–2.1; $p < 0.001$) [33]. Increased sebum secretion does not appear to be associated with the abnormalities of the autonomic nervous system [32] because it is mostly regulated by the endocrine system. Skin biopsies of PD patients have shown numerous α-synuclein aggregates in sebaceous cells. A median of 62.1% of cells in the pilosebaceous unit show positive α-synuclein expression in PD patients compared to 0% for healthy

controls [16]. α-Synuclein could interfere with the production and excretion of sebum in sebaceous glands, resulting in oily or dry skin.

To summarize, our proposed hypothesis states that earlier age at onset of hair greying, greater tendency to sunburn, difficulty tanning and dysregulation of sebum production are more common among PD patients due to genetically determined lower constitutive amounts of eumelanin and α-synuclein accumulation in the skin.

Evaluation of hypothesis

To evaluate our hypothesis we enrolled 32 patients diagnosed with PD and 35 age and gender matched PD-unaffected individuals in a retrospective pilot study. Following approval by the Lithuanian University of Health Sciences Bioethics Committee, the study was conducted in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics and the Republican Hospital of Kaunas. All patients gave informed consent to participate in the study. Blink rate was measured according to the method described by G. Deuschl et al. [34]; the subjects had to stare at an open cross with 9.5 cm × 9.5 cm side length in a quiet place for two minutes and their blinks were counted by the examiner. A survey was used to collect other data. Study subjects who did not know their skin type were given explanations of each skin type by the investigator. Normal skin type was described as having smooth texture, no flaky or greasy areas, very few imperfections and barely visible pores. Oily skin was characterized as greasy or shiny and accompanied by large pores. Rough, flaky skin which feels tight and even itchy was classified as dry. Combination skin was described as the presence of both dry and oily areas. Tanning poorly was defined as the inability to tan at all or the development of a light tan only after several exposures to the sun; tanning easily was defined as the development of a brown tan sometimes even after a few hours of sun exposure. Burning often was defined as burning always after any unprotected exposure to the sun or after prolonged exposure to the sun; burning rarely was defined as rare burns even after staying in the sun for an extended period. The characteristics of patients included in this pilot study are summarized in Table 1. The median of age at onset of hair greying was 30% lower in the PD group compared to the control group (35 and 50 years, p = 0.002) and the median of blink rate was 46.7% lower in the PD group (8 and 15 times/min, p < 0.001). In addition, PD patients were more likely to burn easily and tan poorly compared to individuals unaffected by PD. The majority of individuals in the control group (n = 24, 68.5%) had normal skin type, whereas dry and oily skin types were the most prevalent among subjects with PD (n = 14, 43.8% and n = 9, 28.1%, respectively).

Table 1
Characteristics of patients included in the study.

		PD group (n = 32)	Control group (n = 35)	p values
Sex, female		23 (71.9)	27 (77.1)	0.621
Age, years		67.0 (61.3–77.0)	66.0 (61.0–78.0)	0.945
Age at onset of hair greying, years		35.0 (28.0–45.0)	50.0 (33.8–55.3)	0.002
Ability to tan	Tans easily	12 (37.5)	24 (68.6)	0.035
	Tans poorly	11 (34.4)	7 (20.0)	
	Not sure	9 (28.1)	4 (11.4)	
Tendency to burn	Burns often	21 (65.6)	10 (28.6)	0.001
	Burns rarely	9 (28.1)	25 (71.4)	
	Not sure	2 (6.3)	–	
Skin type	Dry	14 (43.8)	6 (17.1)	< 0.001
	Normal	5 (15.6)	24 (68.6)	
	Oily	9 (28.1)	3 (8.6)	
	Combination	4 (12.5)	2 (5.7)	
Blink rate, times/min		8.0 (5.3–11.0)	15.0 (11.0–21.0)	< 0.001

Quantitative variables are presented as median (interquartile range). Categorical variables are presented as count (percentage). PD = Parkinson's disease.

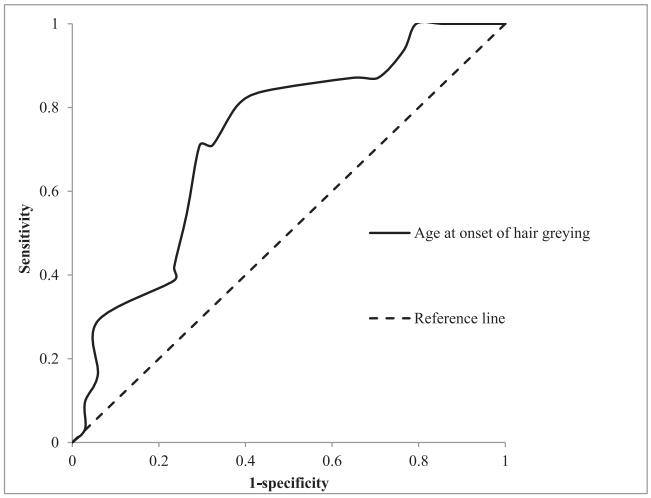

Fig. 1. Receiver operating characteristic curve for the ability of age at onset of hair greying to predict Parkinson's disease.

Receiver operating characteristic curve analysis (Fig. 1) showed that the optimal cut-off value for the ability of age at onset of hair greying to predict PD was ≤ 41 years with 71.0% sensitivity and 70.6% specificity; area under curve was 0.725 (95% CI = 0.601–0.850, p = 0.002).

Consequences of the hypothesis and discussion

Our results support the hypothesis that PD is associated with earlier age at onset of hair greying, greater tendency to sunburn, difficulty tanning and non-normal skin type. It is most likely that earlier hair greying and dysregulation of sebum production are pre-motor features of PD, whereas higher sensitivity to UV radiation could be both a risk factor for PD and a pre-motor symptom.

The importance of identifying risk factors and pre-motor symptoms of PD lies in the value of early PD diagnosis and initiation of potential neuroprotective treatment. Multiple potential disease-modifying therapies are under investigation; however, they can only halt the loss of SN dopaminergic neurons, which is approximately 30% at the time of the emergence of motor symptoms [4]. Subjects identified 3–5 years before they are currently diagnosed may be an ideal group for neuroprotective trials [35]. Currently the best characterised early non-motor features of PD are idiopathic olfactory dysfunction and RBD [35]. The former is highly prevalent among PD patients and it is estimated that 96.7% of them present with significant olfactory loss when compared to young normosmic subjects [36]. However, despite being highly sensitive, olfactory dysfunction is non-specific for PD because 24.5% of 53–97-year-olds have olfactory impairment and the prevalence increases with age, reaching 62.5% for individuals older than 80 [37]. The prevalence of RBD among PD patients is lower compared to olfactory dysfunction and ranges from 19 to 70% with an estimated pooled prevalence of 42.3% [37], but it is much more specific because more than 80% of patients diagnosed with RBD eventually develop a neurodegenerative disorder, predominantly PD [38,39]. However, these two clinical features are not sufficient to predict PD. Multiple risk factors and early non-motor symptoms could be combined to create an accurate formula estimating the risk of developing PD. The PREDICT-PD risk score was proposed to identify individuals at high risk of PD [40], but a prospective study revealed that it only slightly improves long-term prediction of PD [41].

One of the factors which could be included in a risk-score model to identify individuals at high risk of PD is decreased blink rate, which is a

well-known motor feature of PD [42]. We observed 46.7% lower median of blink rate among PD patients. Because decreased blink rate has been reported not only in later stages of the disease, but even among patients with early untreated PD [43], it might precede the manifestation of the cardinal motor symptoms of PD, i.e., rest tremor, bradykinesia and rigidity; however, this hypothesis could be evaluated only in a prospective study.

Our main hypothesis was that lower skin phototype, earlier onset of hair greying and dysregulated sebum production are associated with PD. The results of this pilot study indicate that this hypothesis seems plausible; however, all PD patients irrespective of their disease stage and treatment received were included in this study and this poses a problem when evaluating the results regarding skin type. Dysregulated sebum production was present in the majority of PD patients: 43.8% of them reported having dry skin and 28.1% had oily skin. Accumulation of α-synuclein in the skin could interfere with the function of sebaceous glands, resulting in non-normal skin type; however, sebum production might also be affected by antiparkinson drugs. One study showed that both bromocriptine and combined therapy with L-dopa and benserazide reduce male sebum excretion rate as early as 7 days after the initiation of treatment [44]; however, another study found no decrease in sebum excretion rate six months after the initiation of treatment with L-dopa or L-dopa and dopamine receptor agonist [32]. For this reason, sebum secretion might be dysregulated due to PD per se or because of the effects of antiparkinson medications.

Unfortunately, the reliability of our results is undermined by a small sample size and case-control design; nevertheless, this study provides ideas worthy of further investigation. If additional studies support our hypothesis, skin and hair features could be included in a risk-score model to identify individuals at high risk of PD with the eventual aim to diagnose PD in the pre-motor stage and initiate potential neuroprotective treatment.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.04.013.

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